

REMARKS

Applicant previously canceled Claims 27 and 32 without prejudice or disclaimer. Applicant has canceled Claims 31 and 33-59 herein without disclaimer or prejudice, as being drawn to non-elected inventions. Applicant reserves the right to prosecute the subject matter of these claims in one or more continuation or divisional applications.

Applicant has canceled Claims 14 and 17 without prejudice or disclaimer, and has amended Claims 1, 6, 8, 22, 26, 28, and 30 for clarity herein. Enabling support for these amendments can be found in the application as filed (*See, e.g.*, original claims, Examples 3-5). Therefore, no new matter is contained in the amendments. Applicant notes that the term "tumorigenesis" has been deleted from the claims; however, as the pending claims are directed to methods of inhibiting angiogenesis, the claims clearly encompass the inhibition of tumorigenesis. Reconsideration of the present application and allowance of resulting Claims 1-13, 21-26, and 28-30 are respectfully requested in view of the amendments and following remarks.

Applicant also has withdrawn Claims 15, 16, and 18-20 as being drawn to non-elected species or non-elected nested species. Therefore, because the claims as they relate to the elected species and nested species are in condition for allowance, Applicant respectfully requests that the Examiner examine the claims with respect to the next nested species, apelin antisense nucleic acids.

I. Restriction Requirement

The Office Action made final the previous restriction requirement. Accordingly, Applicant has canceled Claims 15-20, 31, and 33-59 without disclaimer or prejudice as being drawn to non-elected inventions. Applicant reserves the right to prosecute the subject matter of these claims in one or more continuation or divisional applications.

II. Sequence Listing/New Matter

The Office Action objected to the Preliminary Amendment of October 7, 2005 requesting entry of a revised Sequence Listing as allegedly raising issues of new matter for SEQ ID NO:11. Applicants respectfully submit that the revised Sequence Listing does not correct an error in the sequence of SEQ ID NO:11, but rather it corrects the label of the sequence. SEQ ID NO:11

discloses a consensus nucleic acid sequence for HIF-1 α (See specification as filed, page 35, paragraph [0116]). The original Sequence Listing submitted on June 11, 2004 incorrectly labeled SEQ ID NO:11 as being an amino acid sequence, as opposed to a nucleic acid sequence. The revised Sequence Listing merely corrected this error in the label. Therefore, as the revised Sequence Listing does not raise a new matter issue, the objection should be withdrawn.

III. Specification

The Office Action objected to the specification because of certain informalities. In particular, the Office Action noted that several trademarks were used in the application and that the trademarks should be capitalized where used. The Office Action also objected to the disclosure of sequences in the specification without sequence identifiers. Applicant respectfully submits that these objections are moot in view of the following remarks and the amendments made herein.

First, Applicant has carefully reviewed the specification for the use of any trademarks and have made appropriate amendments to the specification herein where necessary. Second, Applicant notes that the Preliminary Amendment filed on June 11, 2004, and acknowledged on page 2 of this Office Action, amended the specification to introduce sequence identifiers for the disclosed sequences on page 14, paragraph [043]. Accordingly, Applicant respectfully requests that the objections be withdrawn.

IV. Claim Objections

The Office Action objected to Claim 28 for omitting the term "and" before the final species of the Markush group. Applicant respectfully submits that this objection is moot in view of the amendments made herein. Accordingly, Applicant respectfully requests that the objection be withdrawn.

V. Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-14, 21-26, and 28-30 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite in the recitation of certain terms or phrases. These rejections are moot with respect to Claim 14 because this claim has been canceled herein without prejudice or disclaimer.

Applicant respectfully submits that the pending claims as amended particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claims 1-14, 21-26, and 28-30 were rejected as being indefinite in the use of the phrase "inhibiting angiogenesis or tumorigenesis in a biological sample" because it is allegedly unclear where the biological sample is taken from or obtained, and because the relevance of inhibiting angiogenesis or tumorigenesis in the sample is allegedly unclear. Applicant respectfully submits that a "biological sample" would be understood by one of ordinary skill in the art to be a representative portion of, or representative part obtained from, a living organism. A "sample" is "a representative part ... from a larger whole," and "biological" is defined as being "of or relating to biology or to life and living processes," as defined by the Merriam Webster medical dictionary online. Accordingly, Applicant respectfully submits that the "biological sample" of Claims 1-13 and 21-23 may be a sample taken from or obtained from a patient (e.g., blood, tissue, organ), or it may be a representative part existing within the patient. The biological sample of Claims 24-26 and 28-30 is a representative part existing within the patient.

Claims 1, 2-14, and 21-30 were rejected as allegedly being indefinite for omitting a method step because it was not clear what the biological endpoint or readout is for determining the inhibition of angiogenesis or tumorigenesis in the biological sample. Applicant respectfully submits that a biological endpoint or readout is unnecessary. Moreover, one of skill in the art would understand that there are many different methods by which the level of angiogenesis may be determined. For example, the number of vessels or vascular branching in the samples may be counted, endothelial cell proliferation and/or migration may be measured, tumor size may be measured, etc. (See, e.g., instant specification, Examples 3-5).

Claims 1-14, 21-26, and 28-30 were rejected as being indefinite in the recitation of the term "the sample." Applicant has amended Claim 1 to recite "the biological sample," providing proper antecedent basis to the claim. Accordingly, this rejection is moot.

Claim 4 was rejected as being indefinite in the recitation of the term "APJ" because it is unclear what molecule is intended. Applicant respectfully submits that one of ordinary skill in the art would understand what molecule is intended. As discussed in the instant specification at page 2, paragraph [004], APJ is a G protein-coupled receptor with seven transmembrane domains that is related to the angiotensin receptor. The application further defines APJ by the sequence

identifier SEQ ID NO:17 (*See* instant specification, page 37). Moreover, the literature describing the isolation of APJ does not further define the term "APJ" as being an acronym for anything. *See* O'Dowd *et al.*, 1993, Gene 136:355-360. Accordingly, one of skill in the art would be aware what molecule is intended by the term "APJ," and therefore, this rejection is moot.

Claim 14 was rejected as being indefinite in the recitation of the phrase "and that interacts with APJ" because it is unclear whether the antibody or the polypeptide is contemplated as interacting with APJ. This rejection is moot as this claim has been canceled herein.

Claims 24-30 were rejected in the recitation of the phrase "wherein the biological sample is in a patient" because it is unclear how a sample can occur or be within a patient. As discussed above, for these claims, the "biological sample" is merely "a representative part ... from a larger whole." Therefore, the apelin inhibiting composition is introduced to the patient. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Claims 6 and 30 were rejected as being indefinite in the recitation of the terms "VEGFs" and "FGFs." Applicants have amended the claims to recite the VEGF and FGF species that are known in the art to be "angiogenic factors" (*i.e.*, VEGF (VEGF-A), VEGF-B, VEGF-C, VEGF-D, VEGF-E, PIGF, acidic fibroblast growth factor (FGF-1), basic fibroblast growth factor (FGF-2). Applicant respectfully submits that the present amendments to the claims render this rejection moot.

Applicant respectfully submits that the claims as amended particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Accordingly, Applicant respectfully requests that the rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

VI. Rejection Under 35 U.S.C. § 112, first paragraph (Written Description)

Claims 8 and 14 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the Office Action asserted that the claims are drawn to antibodies and fragments thereof that inhibit apelin activity and that bind to polypeptides having at least 80% or at least 90% identity with the disclosed sequences. The Office Action asserted that the specification does not disclose a single commercial apelin antibody that meets the limitations of the claims. The Office Action also asserted that the

specification does not provide guidance regarding the structure of the apelin peptides or what changes can or cannot be made in variants with at least 80% or at least 90% identity to the disclosed sequences. Applicant respectfully submits that the rejection is moot with respect to polypeptides having at least 80% or at least 90% identity to the disclosed sequences, as Claim 14 and references to such polypeptides in Claim 8 have been canceled herein. Applicant respectfully submits that the pending claims are supported by the specification such that one of ordinary skill in the art would conclude that the Applicant was in possession of the claimed invention.

As mentioned above, the currently pending claims relate to methods of inhibiting angiogenesis through the use of an antibody or fragment thereof that binds an apelin polypeptide (*i.e.*, one of the disclosed sequences) and thereby inhibits the activity of that apelin polypeptide. Although a specific antibody that binds and inhibits the activity of an apelin polypeptide is not disclosed in the specification, one of skill in the art would readily understand that Applicant was in possession of the claimed invention. As discussed in the specification on pages 22-23, paragraph [065]-[067], methods for making antibodies and analyzing their binding specificity are well known in the art. Further, the specification provides additional methods for determining that an antibody or other modulator specifically affects apelin activity and angiogenesis. For example, the effect of the antibody or other modulator may be determined in a chicken chorioallantoic membrane (CAM) assay by measuring vascular branching in the presence or absence of the antibody or other modulator. *See* instant specification, page 26, paragraph [078].

The currently pending claims are supported by the specification such that one of ordinary skill in the art would recognize that Applicant was in possession of the claimed invention at the time of filing of the application. Accordingly, Applicant respectfully requests that the rejections under 35 U.S.C. § 112, first paragraph be withdrawn.

VII. Rejections Under 35 U.S.C. § 112, first paragraph (Enablement)

Claims 1-14, 21-26, and 28-30 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Office Action alleged that the instant specification does not disclose that any apelin activity inhibitor could block angiogenesis or tumorigenesis in a biological sample. Further, the Office Action asserted that the specification

does not disclose a model showing that any apelin inhibitor could be administered to a human patient in order to inhibit angiogenesis or tumorigenesis. Applicant respectfully submits that the specification is sufficient to enable one of ordinary skill in the art to make and use the invention as recited in the currently pending claims.

Applicant respectfully submits that the specification does in fact disclose a model suggesting that an apelin inhibitor could be administered to a human patient in order to inhibit angiogenesis or tumorigenesis. Example 5 shows that an apelin antisense oligonucleotide inhibits angiogenesis in the angiogenesis model system of *Xenopus* embryos. See instant specification, pages 33-34, paragraphs [0106]-[0112]. This model system is an art-accepted angiogenesis model system:

Xenopus laevis is an extremely useful model organism in which to study the processes and factors involved in both vasculogenesis and angiogenesis. *Xenopus* embryos possess significant clarity during vascular development and allow observation of almost the entire vascular tree. Further, it has previously been established that *Xenopus* share a greater vascular similarity with higher vertebrates than do other model systems, such as zebrafish. For example, *Xenopus* embryos have septated atria, lungs, defined heart valves, a mammalian-like pattern of tail vasculature, blood islands, and a vitelline network (Kolker et al., 2000; Mohun et al., 2000; Cleaver et al., 1997; Millard, 1949; Aoyama, 1956; and Kau and Turpen 1983). In *Xenopus*, as in higher vertebrates, the earliest stages of vascular development involve angioblast induction in the mesoderm of embryos (reviewed in Cleaver et al., 1999). While several experiments suggest that angioblasts can arise from most presumptive gastrula-stage mesoderm (Noden et al., 1989; Devic, 1996; and Mills et al., 1999), the major population of angioblasts in *Xenopus* embryos arises in the dorsal lateral plate mesoderm during neurula stages, as indicated by *in situ* hybridization with the angioblast markers flk-1 and x-msr (Cleaver et al., 1997; Devic, 1996, reviewed in Cleaver et al., 1999).

Levine et al., 2003, Develop. Biol. 254:50-67 at page 50, second column, bridging paragraph.

In the present specification, apelin antisense morpholino oligonucleotides (or mismatch controls) were injected into one cell of a 2 cell frog embryo along with Texas Red as a lineage tracer. Embryos were grown to stage 35 and then assayed by *in situ* hybridization using the vascular marker erg. The antisense oligos resulted in a 67% inhibition of angiogenic growth of embryonic blood vessels, including inhibition of the development of the intersomitic vessels (See Figure 9 of instant specification). Similar results were obtained with antisense oligonucleotides to the APJ receptor; however, mismatch control oligonucleotides did not detectably affect the

vascular growth of the embryos. These results show that the apelin antisense molecules specifically inhibit angiogenesis in an art-accepted model system for angiogenesis.

Moreover, the specification clearly enables the use of antibodies or fragments thereof that specifically bind and inhibit apelin activity. As discussed above, the specification notes that methods for making antibodies and analyzing their binding specificity are well known in the art. See pages 22-23, paragraph [065]-[067]. In fact, antibodies were known at the time of filing that specifically bind apelin. See, e.g., Kleinz and Davenport, 2004, *Regulatory Peptides* 118:119-25.

In addition, Applicant has identified antibodies that specifically bind and/or inhibit apelin activity. See Declaration of Paul A. Krieg (attached). Specifically, Applicant has identified an apelin antibody that specifically inhibits angiogenesis in the CAM assay, an art-accepted angiogenesis model. In these experiments, 10 day old chicken chorioallantoic membranes (CAMs) were used. Twelve CAMs were treated for each group at the start of the experiment. After 72 hours, the CAMs were collected, and the number of blood vessel branches were scored. The results clearly demonstrate that the specification is enabling for methods of using apelin antibody to inhibit angiogenesis in a biological sample. See Exhibit B.

For at least the foregoing reasons, Applicants respectfully submit that the specification is sufficient to enable one of ordinary skill in the art to make and use the invention as recited in the currently pending claims. Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Conclusion

Applicants believe that the present application, as amended, is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The foregoing is submitted as a full and complete response to the Office Action mailed April 19, 2007.

A petition for a two-month extension of time is enclosed, along with the appropriate fee therefor. It is not believed that any additional extensions of time or fees for net addition of claims are required. However, please charge any additional fees that may be due, or credit any overpayment, to Deposit Account 19-5029 (Ref. No.: 20825-0004). In addition, if there are any

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issues that can be resolved by a telephone conference or an Examiner's amendment, the Examiner is invited and encouraged to call the undersigned attorney at (404) 853-8000.

Respectfully submitted,



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